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BRIEF REPORT

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# Vitamin D and Lupus: Are we doing enough?

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**ABSTRACT**

The aim of this study is to identify rheumatology practice care gaps in evaluating for vitamin D deficiency in systemic lupus erythematosus (SLE), as well as adherence to vitamin D replacement in SLE patients currently on corticosteroid therapy. Data for this study were collected from the Southern California Lupus Registry in addition to data extraction from medical health records. Evaluation of serum vitamin D level within 6 months of patient encounter, current or prior use of systemic corticosteroids, and vitamin D replacement in patients receiving corticosteroid therapy were noted. Vitamin D deficiency was defined as serum 25(OH)$D_3$ less than 30 ng/ml. Of 182 patients in the cohort, data were available for 176. Evaluation of vitamin D deficiency was noted in 49 patients (28%), 27 (55%) of whom had abnormal values. Current corticosteroid use was noted in 56 (32%) patients and prior use in 73 (41%). Vitamin D replacement was prescribed to 30 (54%) patients with current corticosteroid use. In an academic rheumatology clinic, we have identified underevaluation for vitamin D deficiency in SLE patients despite increasing awareness of its contribution to disease activity. Further, routine supplementation of vitamin D is particularly lacking in individuals receiving systemic corticosteroids. This presents a practical opportunity for improvement in SLE clinical care.

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Systemic lupus erythematosus; vitamin D deficiency; corticosteroids; disease flare; rheumatology; systemic disease; nutrition

## 1. Introduction

Systemic lupus erythematosus (SLE) is a complex autoimmune disease with a myriad of pathophysiologic pathways. Ongoing work evaluating the impact of vitamin D deficiency on SLE onset and disease activity paves the way for a modifiable treatment option for an otherwise challenging disease.

Vitamin D deficiency is prevalent in the general population, affecting 6% of the USA and more than 20% of the population in India, Tunisia, Afghanistan and Pakistan [1,2]. Data from a population-based cohort of more than 100 patients with SLE demonstrated lower vitamin D levels compared to age-, sex-, season-, and smoking history-matched controls [3]. Due to the association of sunlight and ultraviolet ray exposure with SLE flares, clinicians advise patients to avoid unnecessary sun exposure and to apply sunscreen while outdoors [3,4]. This can hinder the physiological process of ultraviolet B entering the skin and converting 7-dehydrocholesterol to previtamin $D_3$ and subsequently vitamin $D_3$[5]. Furthermore, reduced 1α-hydroxylation of 25(OH)$D_3$ in the setting of renal insufficiency, as well as the use of medications, such as corticosteroids and calcineurin inhibitors can contribute to low vitamin D levels in SLE patients [4,6].

Studies in patients with SLE have attributed vitamin D deficiency to manifestations of cognitive impairment, fatigue, sleep disturbance, cardiovascular disease, and insulin resistance [4–6]. The precise role of vitamin D on the immune system in SLE is not well understood despite the correlation of vitamin D deficiency with disease activity [4,7]. However, several identified mechanisms by which vitamin D interacts with immune cells in SLE are illustrated in Figure 1. Vitamin D can alter immunocyte gene transcription and downstream signaling. Through these signaling pathways, Treg cells are activated resulting in immune regulation and suppression [6,8]. Further downregulation of IL-2 in Th1 cells results in inhibition of IFNγ, while upregulation of Th2 cells suppresses Th17, both of which are important factors in lupus pathophysiology [4,6,9]. Additional anti-inflammatory benefit is noted through suppression of dendritic cell maturation and macrophage-mediated inflammation, as well as decreased B cell proliferation and class switching, thereby affecting immunoglobulin levels [4].

Irrespective of the presence of SLE, the National Health and Nutrition Examination Survey has confirmed the risks of corticosteroid use with severe vitamin D deficiency, emphasizing the importance of addressing vitamin D deficiency within the general population at minimum and particularly in

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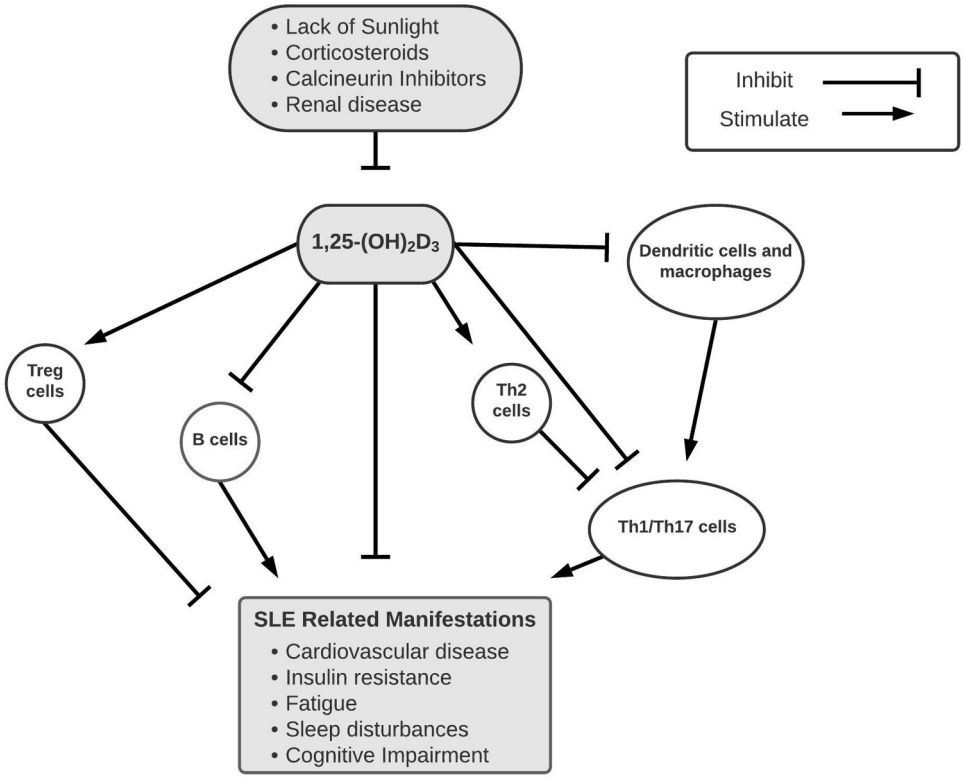


Figure 1. Potential mechanisms involved in the interaction of $1,25(OH)_2D_3$ with the environment, medications, chronic disease, and immune cells in mediating the clinical manifestations of SLE [4].

individuals treated with corticosteroids [10]. While the American College of Rheumatology (ACR) recommends a daily intake of 800–1000 IU of vitamin D in chronic corticosteroid users, the effect of corticosteroids on vitamin D degradation and catabolism may warrant a higher supplementation dose [11–13]. In a longitudinal study of SLE patients with serum $25(OH)D_3$ level below 40 ng/mL, Petri and colleagues demonstrated that increasing the serum vitamin D levels resulted in a modest but significant decrease in SLE clinical disease activity as well as an improvement in urine protein-to-creatinine ratio. These findings have led to a recommended goal serum $25(OH)D_3$ level of greater than 40 ng/mL [14].

The objective of this study is to identify practice care gaps among rheumatologists in evaluating for vitamin D deficiency in SLE as well as their recommendations for vitamin D replacement in SLE patients currently on corticosteroid therapy. Our exploratory hypothesis is that corticosteroid use is associated with vitamin D deficiency.

## 2. Materials and methods

This study was approved by the Institutional Review Board at Loma Linda University and all patients provided written informed consent for participation.

Data was collected from the Southern California Lupus Registry (SCOLR), a cohort of 182 patients with SLE (diagnosed per ACR/SLICC classification criteria) seen at the Loma Linda University Health Rheumatology clinic whose baseline characteristics are described elsewhere [15]. A cross-sectional review of medical records of these patients seen from June 2016 to April 2019 included:

(1) Evaluation of at least one serum vitamin D level within 6 months of patient encounter
(2) Current or prior use of systemic corticosteroids
(3) Vitamin D replacement in patients receiving systemic corticosteroid therapy

Independent review of prescribed medications was completed. Chart review was also completed to ascertain whether vitamin D supplementation was recommended. Vitamin D deficiency was defined by serum $25(OH)D_3 < 30$ ng/mL. Descriptive statistics were utilized.

## 3. Results

Of 182 patients in our SLE cohort, complete data were available to be analyzed in 176 (Figure 2). Serum $25(OH)D_3$ levels were evaluated in 49 (28%) patients within 6 months of the patient encounter. Among patients with available vitamin D levels, none had more than one vitamin D value during this time frame. Vitamin D deficiency was noted in 27/49 (55%) with a mean vitamin D level of 21.6 ng/ml (range, 10.7 to 29.6 ng/ml) in those with a deficiency. Current corticosteroid use was reported in 56/176

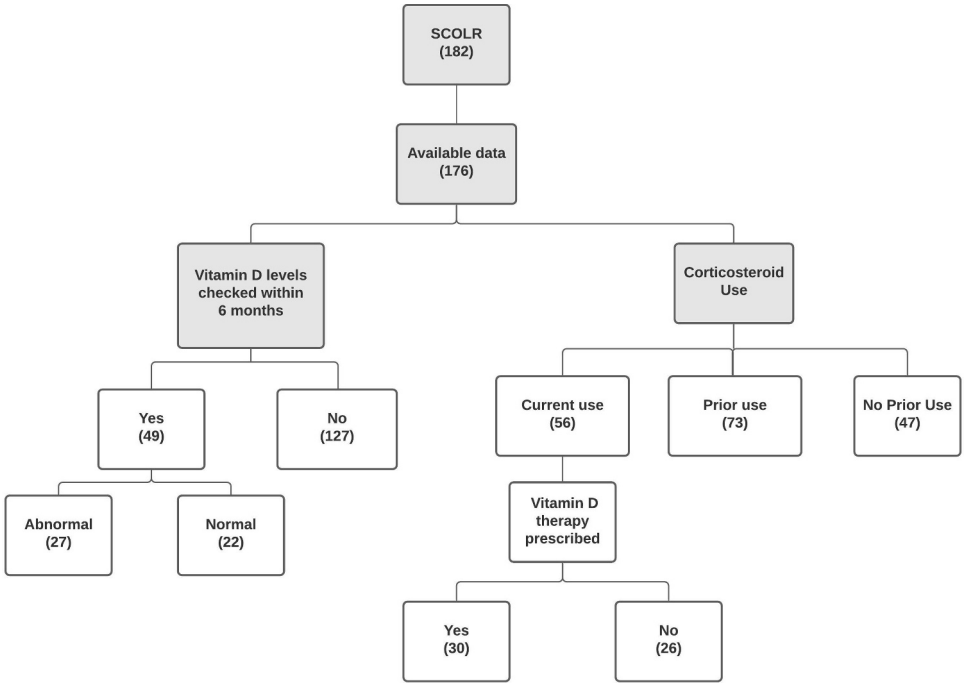


Figure 2. Methodology and Results. (n) patients reported.

Table 1. Serum vitamin D level crosstabulation with corticosteroid use.

| Steroid Use | Vitamin D level checked | | | Vitamin D level not checked |
|---|---|---|---|---|
| | Normal (n) | Abnormal (n) | Total (n) | Total (n) |
| Never | 7 | 12 | 19 | 28 |
| Current | 7 | 7 | 14 | 42 |
| Prior | 8 | 8 | 16 | 57 |
| Total | 22 | 27 | 49 | 127 |

No statistically significant difference in vitamin D levels in those with current and prior use of steroids (n = 30) in comparison to those with no prior use of steroids (n = 19). Pearson Chi [2] test of independence, $X^2$ (1, $N$ = 49) = 1.07, $p$ = 0.899.

(32%) patients and prior use in 73/176 (41%). Forty-seven (27%) patients had no prior use of corticosteroids. In patients currently receiving corticosteroid therapy (n = 56), concomitant vitamin D replacement was prescribed to 30 (54%).

After cross-tabulating current or prior use of systemic corticosteroids with serum 25(OH)$D_3$ levels, we were unable to identify an increased risk of vitamin D deficiency (OR 0.583, 95% CI 0.18–1.89). However, serum 25(OH)$D_3$ was not checked in 42/56 (75%) patients currently on corticosteroids and 57/73 (78%) patients with prior use of corticosteroids (Table 1).

## 4. Discussion

Despite awareness of the impact of vitamin D deficiency on SLE onset and disease activity, we find that rheumatologists are infrequently screening for vitamin D deficiency in patients with SLE. Among our patients with available data, vitamin D levels were obtained in only one third of patients. We can only speculate that this is because something as simple yet impactful as vitamin D can be easily overlooked, despite the awareness, when balancing patients' labs and complex medication regimens. Hence, this study highlights an easily modifiable gap in the care of patients with SLE.

While our analysis did not demonstrate a significant increase in vitamin D deficiency in patients with corticosteroid use compared to those with no prior use of corticosteroids, a serum 25(OH)$D_3$ level was not checked in 99 (77%) patients with current or prior use of corticosteroids and 28 (60%) patients with no prior corticosteroid use, thereby limiting the study power to make more meaningful conclusions. Larger studies have demonstrated a significant association between corticosteroid use and vitamin D deficiency [10]. Furthermore, the role of glucocorticoids in bone resorption, decreased calcium absorption, and the upregulation of 24-hydroxylase activity contributing to vitamin D catabolism is known [13]. Therefore, we acknowledge the need for regular monitoring of vitamin D levels in SLE patients that are taking glucocorticoids.

Our findings have paved the path to implementing a best practice advisory (BPA) warning in the electronic medical records of all individuals with SLE without a serum 25(OH)$D_3$ level within 6 months. This BPA will prompt the provider to obtain a vitamin D level and initiate therapy at minimum in individuals with serum 25(OH)$D_3$ < 30 ng/mL thereby promoting timely intervention and better outcome in this patient population. We also encourage attendings, fellows, and

residents to discuss the impact of vitamin D on SLE in their clinics so as to bring more awareness around the topic and serve as a reminder to check for and to prescribe vitamin D replacement in their lupus patients. Additional attention is warranted in monitoring and replacing vitamin D as a complementary treatment of SLE, which will be studied further as a continuation of this analysis.

We recognize the limitations of our analysis, particularly that this study was conducted by chart review alone and, unless documented in the record, we were unable to clarify whether or not patients were receiving over the counter vitamin D supplementation. We were also unable to confirm serum 25(OH)$D_3$ values in individuals obtaining external labs not interfaced with the electronic medical record. Furthermore, we understand that there are multiple concomitant factors such as antiphospholipid syndrome and osteoporosis that may be of interest in patients with SLE and vitamin D deficiency, but we were either unable to confirm these diagnoses in our patients or the data was not available. Given the small number of patients with available vitamin D levels, we could not perform subanalyses without further compromising power. We plan to expand our current dataset for longitudinal subanalyses with stratified glucocorticoid levels to determine which groups of patients are at highest risk of vitamin D deficiency and which patients warrant routine supplementation. Because the focus of this study was to identify whether rheumatologists at an academic institution are evaluating for and managing vitamin D insufficiency or deficiency in patients with SLE, we did not address the dose of vitamin D supplementation, which also warrants further evaluation. Studying the impact of various supplementation doses for vitamin D deficiency in SLE and its impact on disease activity, fatigue scoring systems, and health associated quality of life measures may prove beneficial in an era of identifying naturopathic approaches to disease control.

SLE is a challenging condition that can lead to decreased quality of life and life-threatening disease flares. The prevalence of vitamin D deficiency in the SLE community and its known immunomodulatory effects on disease manifestations calls for more regular monitoring of this modifiable factor. We hope that our findings will further sensitize researchers and clinicians alike to the need for improved testing for and management of vitamin D deficiency as a means of improving long-term outcomes in SLE.

## Disclosure statement

No potential conflict of interest was reported by the author(s).

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